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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/543,048	01/26/2006	Philipp Hadwiger	051058-73000	3878
84717 LeClairRyan 2318 Mill Road Suite 1100 Alexandria, VA 22314	7590 01/18/2011		EXAMINER CHONG, KIMBERLY	
			ART UNIT 1635	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/543,048

Applicant(s)

HADWIGER ET AL.

Examiner

KIMBERLY CHONG

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 November 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 86,94-98,100-102,110,111 and 114-119 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 86,94-98,100-102,110,111 and 114-119 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Status of the Application

Claims 86, 94-98, 100-102, 110, 111 and 114-119 are pending and are currently under examination. Rejections and/or objections not reiterated from the previous office action mailed 11/12/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Priority

Applicant does not receive the benefit of the earlier foreign application Germany 10302421.2 filed 01/21/2003 because the prior applications do not provide adequate support for the claims of the instant application and thus applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120.

The instant application does not receive the benefit of the earlier filed priority document because the instantly recited limitation of the logKow exceeding 1, 1.5, 2 or 3 is not recited. If Applicant believes the prior application provides support then applicant must point, with particularity, to where such support can be found in the specification of the prior application.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent

application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Response to Arguments

Claim Rejections - 35 USC § 112

The rejection of claims 86, 94-98, 100-102, 110, 111 and 114-119 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn. The claims do not specifically recite the dsRNA has the function of increased lipophilic properties as incorrectly stated in the previous Office action and thus the claimed dsRNA comprising only one lipophilic group is adequately described.

Claim Rejections - 35 USC § 103

The rejection of claims 86, 94-98, 100-102, 110, 111 and 114-119 under 35 U.S.C. 103(a) as being unpatentable over Kay et al. et al. (US 2003/0139363), Fosnaugh et al. (US 2003/0143732), Manoharan, M. (Applicant's IDS 02/13/2006), MacKellar et al. (Nucleic Acids Research 1992) and evidenced by Virta (Tetrahedron 2003) is maintained for the reasons of record.

Applicant's arguments filed 11/01/2010 have been fully considered but they are not persuasive. Applicant argues Fosnaugh et al. is the only reference cited for the proposition that the conjugate can be attached through known biodegradable linkers but

provides too many alternatives and no direction to pursue the path identified by the Examiner. Applicant argues none of the references cited provide one of skill in the art with the motivation to conjugate a lipophilic group at the 5' end of the antisense strand and the reference to Manoharan et al. cannot be used as motivated to attach the conjugate to the 5' end as compared to the 3' end because Manoharan based the efficacy between the 5' end and an unconjugated oligonucleotide and not the 5' end and the 3' end.

This argument is not convincing. Fosnaugh et al. clearly teach a dsRNA can be conjugated with any ligand on either end of a strand which increases the stability and cellular uptake of the dsRNA. Fosnaugh et al. teach the use of biodegradable linkers such as a phosphodiester linkage. Thus the skilled artisan would be motivated to attach a ligand group via a biodegradable linkage for better in vivo application. With respect to which end to attach the ligand, the skilled artisan would have looked to the prior art reference of Manoharan et al. which provides convincing data such that one of skill in the art would want to attach a cholesterol group to the 5' end of a strand.

On page 107, column 1 starting in the first full paragraph, Manoharan et al. teach it has been shown in the art that an oligonucleotide with a 5' end cholesterol conjugated group inhibited the expression of MDR associated proteins and the effectiveness of the cholesterol conjugate appears to be due to its rapid and increased cellular uptake. While the second full paragraph on page 107, as pointed out by Applicant, demonstrates a 3' cholesterol conjugated oligonucleotide has an increased cellular uptake and efficacy against the p75 nerve growth factor receptor when used in vitro as

compared to a 5' cholesterol conjugated oligonucleotide, a bis-cholesterol (5' and 3')-conjugated oligonucleotide was the most potent. So the skilled artisan would take from this particular example that it is better to conjugate both ends to produce a more potent oligonucleotide, at least for targeting a particular gene such as a p75 nerve growth factor as compared to using a 3' cholesterol conjugated oligonucleotide as argued by Applicant.

Manoharan et al. goes on to teach on page 109, beginning in the first full paragraph, that both the 5' and 3' cholesterol conjugated oligonucleotides were much more lipophilic than unconjugated oligonucleotides when testing for the pharmacokinetics of cholesterol conjugates and while a 3' cholesterol conjugated oligonucleotide was more stable as compared to the other conjugates, it has been shown in the art that a 5' cholesterol conjugated oligonucleotide had a 7 fold higher increase in plasma half-life as compared to the 3' cholesterol conjugate. Further on page 109 in the second column, Manoharan et al. demonstrated that the 5' cholesterol conjugated oligonucleotide binds to serum proteins very efficiently which indicates that this association with serum contributes to an increased uptake into cells. Finally Manoharan et al. demonstrates that the 5' cholesterol conjugated oligonucleotide had a greater in vivo therapeutic efficacy as compared to unconjugated oligonucleotide (see bottom of page 109).

Thus the results provided by Manoharan et al. would motivate the skilled artisan to definitely use a cholesterol group conjugated to an oligonucleotide and provide strong evidence that the 5' end of a strand has greater in vivo therapeutic efficacy. The skilled

artisan in looking to increase the efficacy of an oligonucleotide would want to conjugate a cholesterol group at the 5' end.

Even more motivation to conjugate a lipophilic group at the 5' end is provided by at least Virta et al. Applicant argues that Mackellar et al. and Virta et al. only provide a general synthetic strategy of oligonucleotide conjugates and fails to teach or suggest the lipophilic conjugate method to an antisense strand in a dsRNA agent. In response, Mackellar et al. was cited for the knowledge that the general synthetic strategy of oligonucleotide conjugates was well known in the prior art, particularly the use of cholesterol conjugation on either end of an oligonucleotide. Virta et al. provide the motivation to conjugate on the 5' end of a strand. The skilled artisan with the knowledge of Manoharan et al. and compelling evidence that conjugation of a cholesterol group to the terminal ends of an oligonucleotide strand increased the efficacy of an oligonucleotide, would look to the prior art for the most efficient methods of conjugation. Mackellar et al. demonstrates the routine nature of conjugation and with Virta et al. demonstrating attachment of a group to the 5' end as being very straightforward as compared to more complicated attachment of the conjugate groups to the 3' end, the skilled artisan would have clearly been motivated to attach a cholesterol moiety to the 5' end of an antisense strand of the dsRNA.

Applicant argues that the two references of Mackellar and Virta are completely silent on the gene silencing activity of the conjugated oligonucleotide much less a comparison of the activity of dsRNA containing a conjugation on either strand or either end of a strand. In response, the claims do not recite any gene silencing activity of the

conjugated dsRNA nor recite any comparisons or advantage to conjugation on the 5' end as compared to the 3' end. Moreover Mackellar and Virta were not cited for the gene silencing activity of an oligonucleotide.

Applicant argues there is no known means for improving the efficiency of RNAi by dsRNA and just because the prior art teaches conjugation methods using antisense oligonucleotides does not mean the same strategy can be used for dsRNA that would have made the oligonucleotide stable and possess gene silencing activity and further various prior art references have shown that the 5' end phosphodiester modification of an antisense strand of a dsRNA completely abolished its activity or at least reduced its activity compared to a dsRNA with an unmodified antisense strand due to blocking the 5'-OH.

Applicant reiterates the argument that one skilled in the art would not have been motivated to modify the 5'-OH of the antisense strand with the expectation that the dsRNA would enable RNAi (page 6-7 of the Response filed 2/12/2010). This argument was addressed in the Final office action mailed 11/12/2009 and reiterated herein.

The skilled artisan would conclude from the prior art that one of skill in the art would be motivated to modify the 5' end of an antisense strand of a dsRNA. Particularly Rana (of record US2005/0020521) who do not teach away from covalently attaching a lipophilic group to the 5' end of the antisense strand of a dsRNA. A summary of the examples disclosed in Rana is provided below in paragraph [0272]:

[0272] Recent studies have shown that synthetic siRNAs containing 5'-OH termini can successfully induce RNAi effects in *Drosophila* embryo lysates (Elbashir et al., 2001c; Nykanen et al., 2001) and cultured mammalian cells (Elbashir et al., 2001a). A model involving a 5' end kinase activity necessary for RNA interference has been proposed (Nykanen et al., 2001). However, there is no evidence that the 5' end hydroxyl is required for in vivo interference activity. The above results show that

replacing the 5' OH, a kinase target site, with amino groups inhibited RNAi activity. Further isolation of siRNA by biotin pull out experiments revealed that prior phosphatase activity was required for in vitro 5' end radiolabeling by a polynucleotide kinase. Taken together, these results provide strong evidence for the requirement of 5' end kinase activity for RNA interference effects in vivo.

From the studies of Rana and the early prior art on the importance of the 5' end hydroxyl of the antisense strand of a dsRNA, the teachings provide strong evidence that there was a requirement for the 5' end kinase activity for RNAi in vivo however there was "no evidence that the 5' end hydroxyl is required for in vivo interference activity." In other words, at the time of filing of the instant invention it was recognized that the 5' end of the antisense strand of a dsRNA would need to be amenable to 5' end kinase activity but did not necessarily require the OH group present.

This fact has been clearly demonstrated by Schwarz et al., a reference identified by Applicant for the assertion that a free OH must be present on the 5' end of the antisense strand (cited on page 17 of the specification and on the IDS filed 02/13/2006). Schwarz et al. teach that a dsRNA wherein the 5' end of the antisense strand was linked with a 6-amino-hexyl phosphoester was capable of RNAi (see page 544). Therefore, contrary to Applicant's arguments, it was known in the prior art that the 5' end of the antisense strand of a dsRNA did not require a free OH for RNAi and in fact was able to reduce gene expression wherein the 5' end was linked with a phosphodiester group.

Therefore because it was known in the prior art that one can modify the 5' end of the antisense strand of a dsRNA and it was taught by Fosnaugh et al. that conjugation of a ligand at the ends of a dsRNA can increase the efficacy of the molecule and further it was known in the prior art that conjugation of a cholesterol group to the 5' end of an

inhibitory nucleic acid increased the in vivo efficacy of such molecule, it would have been obvious to conjugate the 5' end of the active strand i.e. the antisense strand, of the dsRNA that is responsible for mediating RNAi.

Applicant argue they have surprisingly discovered that covalently linking a lipophilic group thru a phosphodiester linker to the 5' end of the antisense strand of a dsRNA is actually stable and maintains or even improves the RNA interference activity and the biological activity of the dsRNA compared to the unconjugated control.

In response as stated in the previous Office action, while Figure 3 does in fact show a dsRNA of the claimed invention having a cholesterol attached at the 5' end and shows what appears to be a reduction of expression of a B-gal gene up to 20% as compared to the control, the data also show that the same dsRNA with a cholesterol attached at the 3' end showed an even greater reduction in gene expression as compared to the control. Thus, from the data, there does not appear to be an advantage or unexpected superior results as submitted by Applicant as the evidence does not support the arguments that conjugation of cholesterol at the 5' end allows the dsRNA to have increased uptake and unexpected results as compared to a dsRNA molecule with a conjugate at the 3' end. This discrepancy is also shown in Example 7 wherein the specifications discloses a dsRNA with a lipophilic group attached at the 5' end of the sense strand, which is not the complementary strand as claimed, had "superior efficacy and selectivity".

Applicant counters Examiner's conclusion by arguing that the specification as well as in various references it is shown that the phosphodiester modification of an

antisense strand of a dsRNA of a lipophilic group completely abolished or at least reduced its activity. The Examiner has not been able to find these references and therefore cannot completely address the argument. Further, a showing of unexpected results needs to come from the Applicant's specific embodiments and from the results pointed out by Applicant, the results are what have been shown in the prior art and what is expected when conjugating a cholesterol group to the 5' end of an oligonucleotide: a more effective inhibitory nucleic acid molecule as compared to an unconjugated molecule. Therefore Applicant's arguments of unexpected results are not supported by the claims and instant specification.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact Acting SPE for 1635 Heather Calamita at 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Kimberly Chong/
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